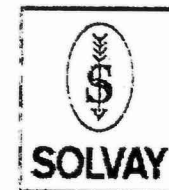
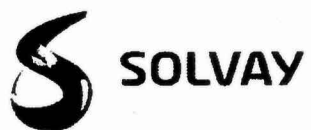


**Thorofare Voluntary Monitoring Program**

**Phase One & Two Aggregate Results**

Solvay  
Solexis





Sincerely,

A handwritten signature in black ink, appearing to read 'Geoff Pass'.

Geoff Pass  
Plant Manager  
Solvay Specialty Polymers USA, LLC

Attachment: Serum Sampling Results

# Phase One & Phase Two

## Range of Aggregate Results

---

- **Phase One**

- C8 < 10 ppb to 5060 ppb
- C9 < 1 ppb to 7080 ppb

- **Phase Two**

- C8 < 10 ppb to 2810 ppb
- C9 < 1 ppb to 2550 ppb

- **Serum levels in general population**

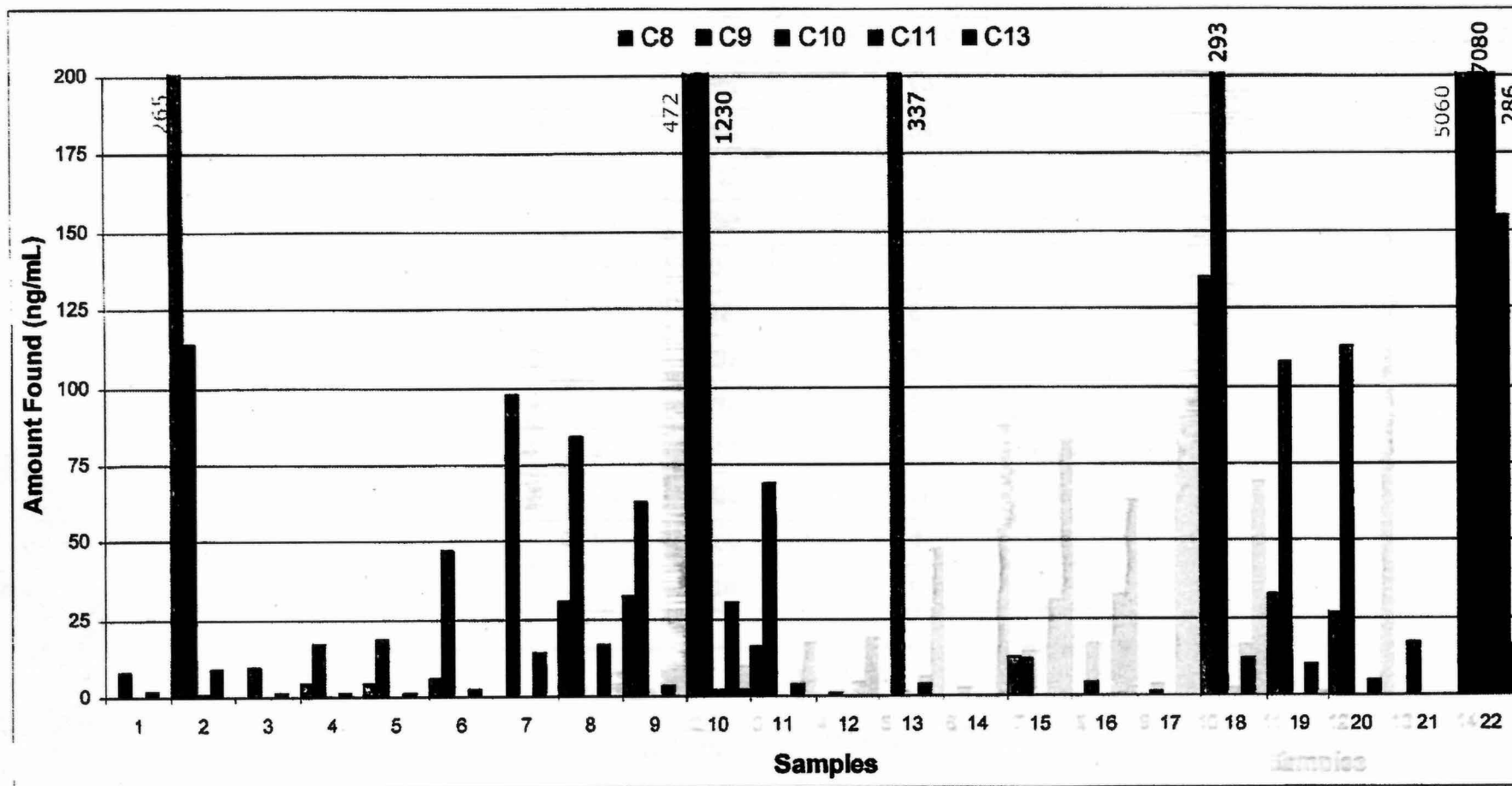
- C8 ~ 6 ppb
  - C9 ~ 1 ppb
-



**Thorofare  
Voluntary  
Monitoring  
Program -  
Phase One  
Results**

	C8	C9	C10	C11	C13
1	<10	8.3	<1.00	2.15	<1.00
2	265	114	1.08	9.18	<1.00
3	<10	9.45	<1.00	1.56	<1.00
4	4.39	17.2	<1.00	1.48	<1.00
5	4.79	18.5	<1.00	1.4	<1.00
6	6.31	47	<1.00	2.35	<1.00
7	<10	97.9	<1.00	14.3	<1.00
8	30.9	84.3	<1.00	16.7	<1.00
9	32.3	63	<1.00	3.52	<1.00
10	472	1230	2.1	30.2	1.85
11	16.3	69	<1.00	4.1	<1.00
12	<10	1.23	<1.00	<1.00	<1.00
13	<10	337	<1.00	4.29	<1.00
14	<10	<1.00	<1.00	<1.00	<1.00
15	12.5	12	<1.00	<1.00	<1.00
16	<10	4.62	<1.00	<1.00	<1.00
17	<10	1.73	<1.00	<1.00	<1.00
18	135	293	<1.00	12.3	<1.00
19	32.7	108	<1.00	10.1	<1.00
20	26.6	113	<1.00	4.84	<1.00
21	<10	17.4	<1.00	<1.00	<1.00
22	5060	7080	286	155	16.1

# Thorofare Voluntary Monitoring Program Phase One Results

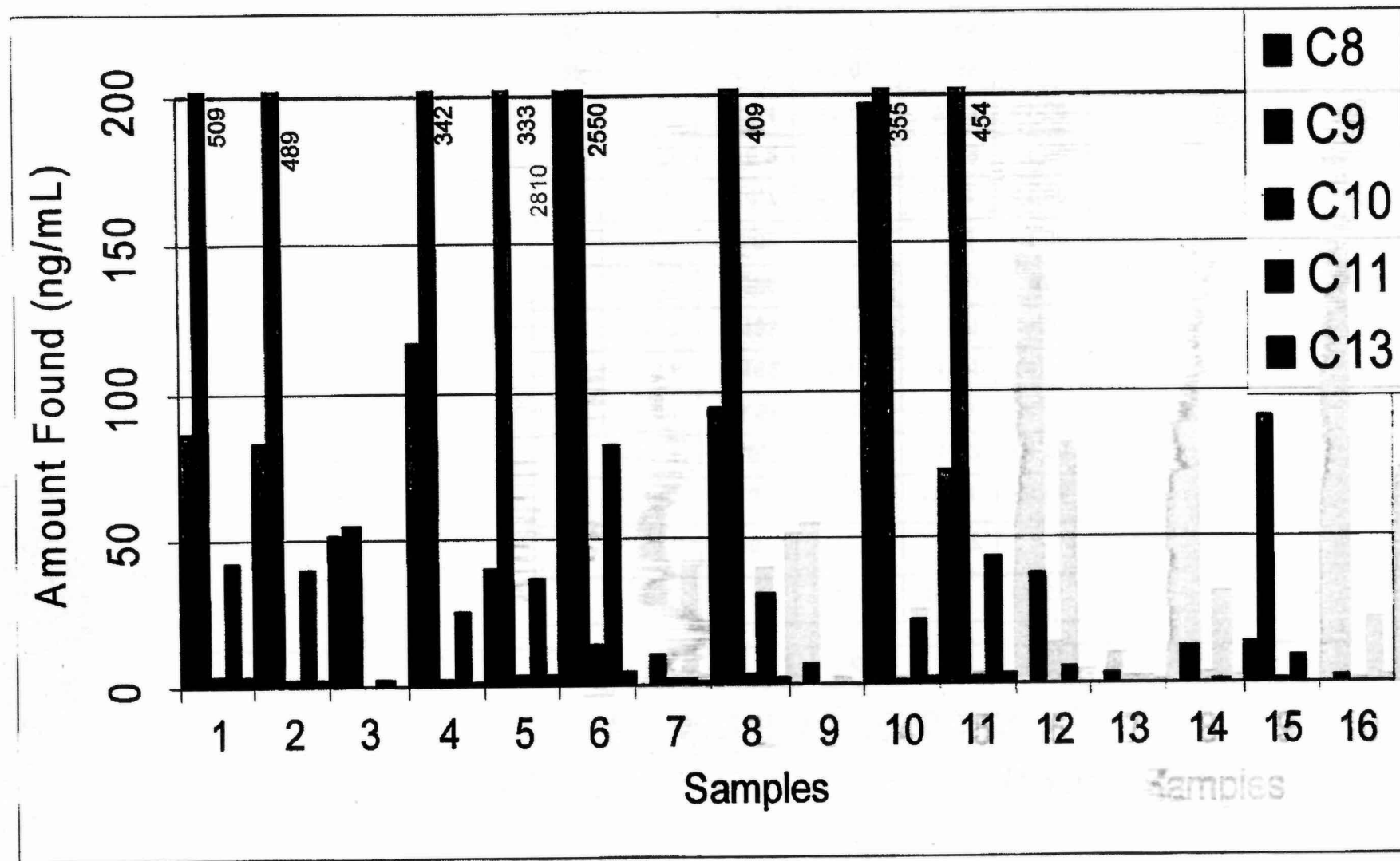


# Thorofare Voluntary Monitoring Program - Phase Two Results

## 1-16

C1	C2	C10	C11	C7	C8	C9	C10	C11	C13
85.4	505	2.97	41.5	1	86.4	509	2.97	41.5	2.88
82.8	486	2.34	39.4	2	82.8	469	2.34	39.4	2.78
51.2	54.6	<1.00	1.74	3	51.2	54.6	<1.00	1.74	<1.00
116	342	2.25	25.2	4	116	342	2.25	25.2	1.53
39	333	3.21	35.7	5	39	333	3.21	35.7	3.79
2810	2550	13.6	81.4	6	2810	2550	13.6	81.4	4.56
<10.0	10.3	2.28	2.67	7	<10.0	10.3	2.28	2.67	1.2
93.7	409	3.2	30.5	8	93.7	409	3.2	30.5	1.95
<10.0	6.77	<1.00	<1.00	9	<10.0	6.77	<1.00	<1.00	<1.00
197	355	1.59	21.6	10	197	355	1.59	21.6	1.71
72.5	454	2.42	42.7	11	72.5	454	2.42	42.7	3.24
<10.0	37.3	<1.00	6.18	12	<10.0	37.3	<1.00	6.18	<1.00
<10.0	2.92	<1.00	<1.00	13	<10.0	2.92	<1.00	<1.00	<1.00
<10.0	12.3	<1.00	1.66	14	<10.0	12.3	<1.00	1.66	<1.00
13.4	90.3	1.17	9.47	15	13.4	90.3	1.17	9.47	<1.00
<10.0	2.03	<1.00	<1.00	16	<10.0	2.03	<1.00	<1.00	<1.00

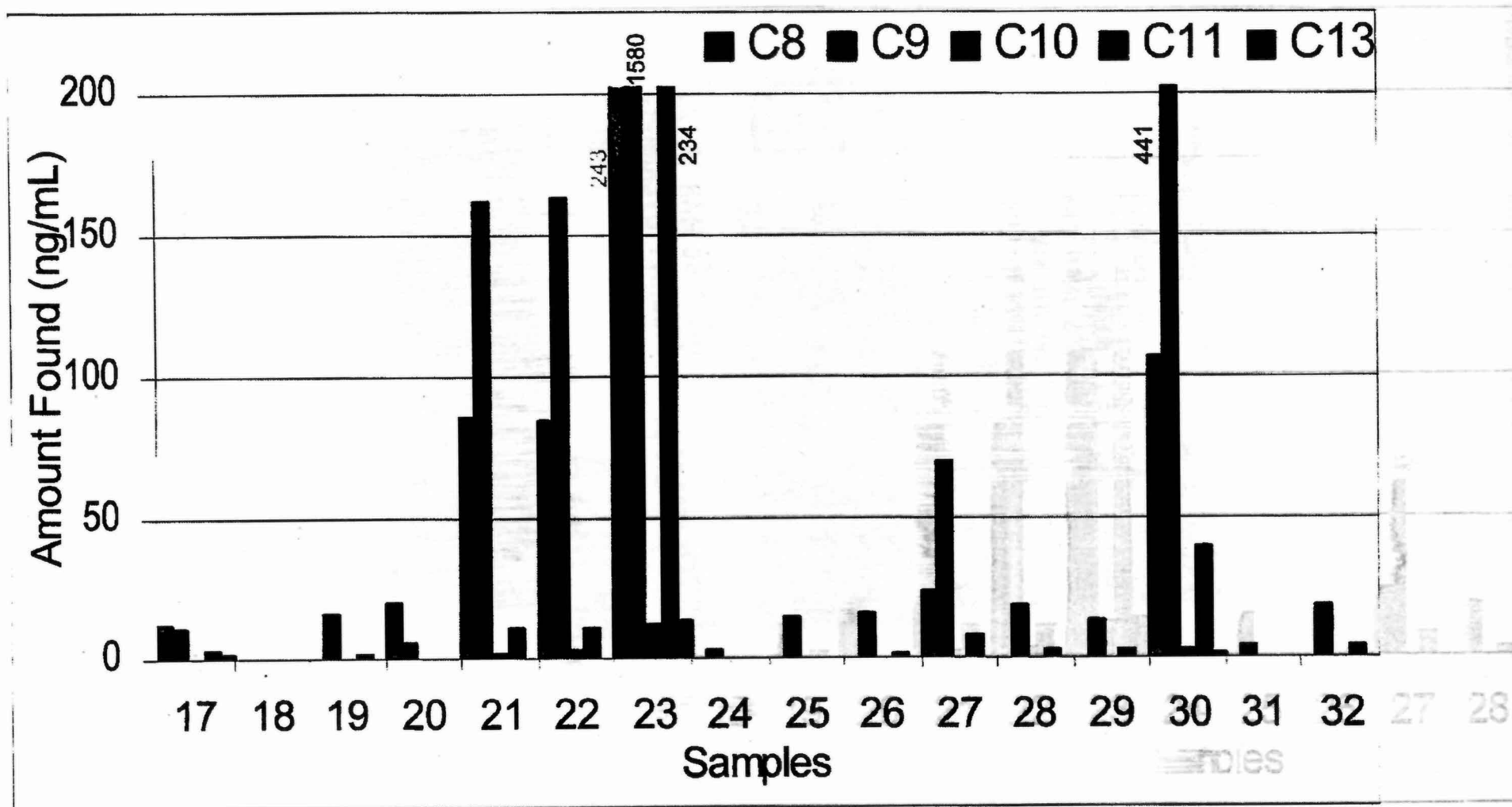
# Thorofare Voluntary Monitoring Program - Phase Two Results 1-16



# Thorofare Voluntary Monitoring Program - Phase Two Results 17-32

	C8	C9	C10	C11	C13
<b>17</b>	11.5	10.2	<1.00	2.47	1.2
<b>18</b>	<10.0	<1.00	<1.00	<1.00	<1.00
<b>19</b>	<10.0	15.3	<1.00	1.02	<1.00
<b>20</b>	19.9	5.55	<1.00	<1.00	<1.00
<b>21</b>	85.8	162	1.15	11.1	<1.00
<b>22</b>	83.9	163	2.35	11	<1.00
<b>23</b>	243	1580	12.1	234	13.6
<b>24</b>	<10.0	2.82	<1.00	<1.00	<1.00
<b>25</b>	<10.0	14.7	<1.00	<1.00	<1.00
<b>26</b>	<10.0	16.2	<1.00	1.29	<1.00
<b>27</b>	23.4	69.4	<1.00	7.56	<1.00
<b>28</b>	<10.0	18.2	<1.00	2.65	<1.00
<b>29</b>	<10.0	12.7	<1.00	2.53	<1.00
<b>30</b>	107	441	2.68	40	1.46
<b>31</b>	<10.0	3.58	<1.00	<1.00	<1.00
<b>32</b>	<10.0	18.9	<1.00	3.7	<1.00

# Thorofare Voluntary Monitoring Program - Phase Two Results 17-32



ORIGIN ID:DYLA (856) 251-3404  
KATHLEEN MEEHAN  
SOLVAY SOLEXIS, INC.  
10 LEONARD LANE

WEST DEPTFORD, NJ 08086  
UNITED STATES US

SHIP DATE: 05MAR14  
ACTWGT: 0.2 LB  
CAD: 0943884/CAFE2704

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WASHINGTON DC 200043302

(202) 564-8840

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**SOLVAY  
SOLEXIS**

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U.S. Environmental Protection Agency  
1201 Constitution Avenue, NW  
Washington, DC 20004-3302

11 FEB 22 PM 12:38

8EHQ-0211-18263A

DCN: 88110000147s

**CONTAINS TSCA CONFIDENTIAL  
BUSINESS INFORMATION**

**Re: Solvay Solexis, Inc.; TSCA Section 8(e) Submission for**  
[REDACTED] (CASRN [REDACTED])

Dear Sir or Madam:

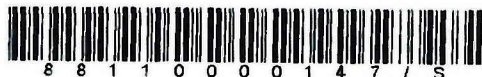
Solvay Solexis, Inc. ("Solexis") hereby submits to the U.S. Environmental Protection Agency ("EPA") under section 8(e) of the Toxic Substances Control Act ("TSCA") information regarding a four-week oral toxicity study in rats using the test substance [REDACTED] with Chemical Abstracts Service Registry Number ("CASRN") [REDACTED].

[REDACTED] also includes  
period of two  
Dawley rats,  
four consecutive  
Experiment 1 for a

date to contact

Enclosure- Attachment 1

cc: Philip Milton, EPA HQ  
Linda Longo, EPA Region 2  
Sandra Podolak, Solvay Solexis Inc.



Solvay Solexis, Inc.  
10 Leonard Lane, West Deptford, NJ 08086  
856 853 8119 Fax 856 853 6405  
www.solvaysolexis.com

**Company Sanitized**



## Summary of Results

[REDACTED] studied the oral toxicity of [REDACTED] when administered daily to rats over a period of four consecutive weeks. Data presented also include observation of recovery from any potential treatment-related effects over a period of two consecutive weeks. Three groups, each of five male and five female Sprague Dawley rats, received the test item by gavage at dosages of 0.3, 0.8 and 2.0 mg/kg/day for four consecutive weeks. Observations were recorded during dosing and at necropsy.

Data present signs of dose-related adverse toxic effects, some of which were not reversible up to two weeks following termination of exposure. The main target organ is the liver findings reported were: hepatocytic, hypertrophy, and necrosis observed only in some males of the high and intermediate dose groups. Only partial remissions of such changes were observed in animals after recovery period. Lung toxicity (characterized by macrophage aggregation); thymus toxicity (characterized by atrophy); and reproductive organ toxicity (manifested by seminal vesicle colloid depletion) were observed in the high dose animals with almost complete remission after the 2 week recovery period. The last two changes could be considered secondary effects related to the general poor conditions of the high dose treated animals. Blood toxicokinetic analyses were carried out after single oral dose of 2.0 mg/kg; the half lives were higher in males than in females.

treatment-retained ef-  
fects and five groups  
0.8 and 2.0 mg/kg  
and at necropsy.

Data presented at the 1990 symposium were reversible up to two weeks after treatment with lindane (100 mg/kg) in the rat. In contrast, the high non-integrated effects of lindane in the animals after recovery from the acute effects of toxicity (characterized by a lymphoid atrophy and vesicle colloid depletion) were observed after the 2 week recovery period. The effects related to the general poor health of the animals after lindane treatment were not observed in the toxicokinetic analyses were carried out. The results were higher in males than in females.



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March 5, 2014

**Via Courier**

CBIC Control Number

**358813**

TSCA Confidential Business Information  
Center (7407M)

EPA East - Room 6428

Attn: Section 8(e)

U.S. Environmental Protection Agency

1201 Constitution Avenue, N.W.

Washington, DC 20004-3302

**Re: Solvay Specialty Polymers USA LLC; TSCA Section 8(e) Submission  
for Chemical Abstract Services Registry Numbers ("CASRN") 335-  
67-1, 375-95-1, 335-76-2, 2058-94-8 and 72629-94-8**

Dear Sir or Madam:

Solvay Specialty Polymers USA LLC ("SSPUSA") hereby submits to the U.S. Environmental Protection Agency under Section 8(e) of the Toxic Substances Control Act ("TSCA") information regarding the results of limited human serum sampling conducted at SSPUSA's facilities located in Thorofare, New Jersey, Hillsborough, New Jersey, and Marshallton, Delaware. The serum samples were analyzed for five substances used at one or more of the plants. Specifically, the targeted analytes were Perfluorooctanoic Acid (CASRN 335-67-1; "C8"), Perfluorononanoic Acid (CASRN 375-95-1; "C9" or "PFNA"), Perfluorodecanoic Acid (CASRN 335-76-2; "C10"), Perfluoroundecanoic Acid (CASRN 2058-94-8; "C11") and Perfluorotridecanoic Acid (CASRN 72629-94-8; "C13").

In 2006-07, SSPUSA (then known as Solexis) collected and analyzed 52 human serum samples. The samples were collected in two phases. The first phase involved 22 samples and was intended as a test run of the protocols to be used for sample collection and data management that would be used in a comprehensive biomonitoring study. Twenty-eight managerial and supervisory personnel were invited to participate in phase one, with 22 ultimately providing serum samples. The phase one group included several individuals with work histories > 25 years in fluoropolymer manufacturing. The results showed the following range of analyte levels: C8: < 10 ppb to 5060 ppb; C9: < 1.00 ppb to 7080 ppb; C10: < 1.00 ppb to 286 ppb; C11: < 1.00 ppb to 155 ppb; and C13: < 1.00 ppb to 16.1 ppb.

Participation in the second phase of the study was open to all Solexis employees at the Thorofare site. It is estimated that 165 employees were employed at that site and,

SOLVAY SPECIALTY POLYMERS USA, LLC

10 Leonard Lane, West Deptford, NJ 08086, USA - T: +856 853 8119 - F: +856 853 6405

www.solvay.com



therefore, were eligible to participate, but only 30 individuals agreed to participate.<sup>1</sup> In general, only a few employees who work in manufacturing areas of the plant volunteered to participate; most volunteers were administrative, laboratory and management employees. The following range of analyte levels were found: C8: < 10 ppb to 2810 ppb; C9: < 1.00 ppb to 2550 ppb; C10: < 1.00 ppb to 13.6 ppb; C11: < 1.00 ppb to 234 ppb; and C13: < 1.00 ppb to 13.6 ppb.

Given the overall low participation rate, including very few employees who spend any significant time in manufacturing areas of the plant, it was decided not to proceed with the study; other than preparing the attached report summarizing the serum measurements generated by Exygen Research, the laboratory that analyzed the sampled blood, no further analysis of the data was conducted. Given the limited amount of data collected, the absence of any analysis of the information, the fact that the other industrial user of PFNA, Arkema, Inc., had recently completed a significant epidemiological study that included blood monitoring,<sup>2</sup> and the fact that Solexis had actual knowledge that EPA had already been briefed on the Arkema study results,<sup>3</sup> the information being provided was not viewed as subject to reporting under Section 8(e) when it was generated.<sup>4</sup> However, in light of enforcement positions EPA has recently taken, SSPUSA is making this submission out of an abundance of caution.

If you have any questions or require additional information regarding this submission, please do not hesitate to contact me.

<sup>1</sup> SSPUSA collected duplicates for two samples, thus bringing the total number of samples in the second phase to 32.

<sup>2</sup> Mundt D.J., Mundt K.A., Luippold R., Schmidt M., Farr C., "Clinical Epidemiological Study of Employees Exposed to Perfluorononanoic Acid (PFNA)," *BOOK OF ABSTRACTS*, 28<sup>th</sup> International Congress on Occupational Health, Milan, Italy, June 11-16, 2006.

<sup>3</sup> Arkema provided an updated presentation to EPA on January 9, 2006, that included discussion of the epidemiology study and the results of blood monitoring. A sanitized copy of the presentation was provided to EPA on June 8, 2006 and is available on [www.regulations.gov](http://www.regulations.gov) at EPA-HQ-OPPT-2003-0012-1090.

<sup>4</sup> Some employees at Solexis sites had years of employment for different companies within the fluoropolymer industry. Given the long half-life of these substances in humans, the lack of information as to the identity of the individuals that provided individual samples, the small number of samples collected, the small number of participating employees who spend any significant time in manufacturing areas of the plant and the absence of associated health histories, the data are not necessarily reflective of historical exposures that may have taken place at any Solvay site. The data are what they are and nothing more.

ORIGINAL

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**SOLVAY  
SOLEXIS**

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EPA East - Room 6428

Attn: Section 8(e) Coordinator

U.S. Environmental Protection Agency

1201 Constitution Avenue, NW

Washington, DC 20004-3302



8 E H Q - 1 2 - 1 8 6 1 8

**Re: Solvay Solexis, Inc.; TSCA Section 8(e) Submission for ETHENE, 1,1,2,2-TETRAFLUORO-, OXIDIZED, POLYMD., REDUCED, ME ESTERS, REDUCED, CASRN 88645-29-8**

Dear Sir or Madam:

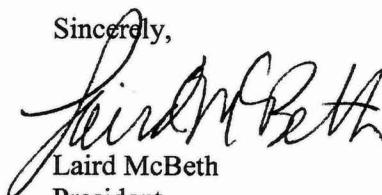
Solvay Solexis, Inc. ("Solexis") hereby submits to the U.S. Environmental Protection Agency ("EPA") under section 8(e) of the Toxic Substances Control Act ("TSCA") information regarding a four-week oral peroxisome proliferation study in rats using the test material (a polymer), ETHENE, 1,1,2,2-TETRAFLUORO-, OXIDIZED, POLYMD., REDUCED, ME ESTERS, REDUCED, with Chemical Abstracts Service Registry Number ("CASRN") 88645-29-8. Solexis (U.S.) received the study on March 2, 2012. While the study is being submitted under Section 8(e), Solexis is not certain that the information is substantial risk information, but is submitting the information under Section 8(e) out of an abundance of caution.

Please see Attachment 1 for a summary of the results.

If you have any questions regarding this submission, please do not hesitate to contact Sandra Podolak at (856) 251-3492.

Sincerely,

Dear Sir or Madam:

  
Laird McBeth  
President

Solvay Solexis, Inc.

Attachment 1

cc: Sandra Podolak, Solvay Solexis, Inc.



8 8 1 2 0 0 0 0 1 6 1

Solvay Solexis, Inc.  
10 Leonard Lane, West Deptford, NJ 08086  
856 853 8119 Fax 856 853 6405  
www.solvaysolexis.com

**CONTAINS NO CBI**



## Attachment 1

### Summary of Results – AST 042/053301

Huntingdon Life Sciences Ltd. (Huntingdon), in Study No. AST 042/053301, studied the peroxisome proliferative effect of the polymer ETHENE, 1,1,2,2-TETRAFLUORO-, OXIDIZED, POLYMD., REDUCED, ME ESTERS, REDUCED when orally administered daily to rats over a period of four consecutive weeks. Livers of animals derived from this study were further analysed for measuring the activity of palmitoyl CoA oxidase. Four groups, each of five male and five female Sprague Dawley rats, received the test item by gavage at dosages of 0, 20, 100, and 500 mg/kg/day for four consecutive weeks. Of those, only 3 animals per group were analysed for the activity of palmitoyl CoA oxidase. Livers were processed and cyanide-insensitive palmitoyl CoA oxidase activity was measured.

Administration of the test substance to rats for 4 weeks produced marked increases in mean palmitoyl CoA oxidase activity in both male and female rats. Increases were dose-related, being approximately twice control activities at the lowest dose level (20 mg/kg/day) and approximately 20-times control activities at the highest dose level (500 mg/kg/day) in male rats and females having approximately 10-times control activities at the highest dose level. In male rats, mean activities were statistically significant from control values at all three treatment levels. In female rats, increases were statistically significant from control values at the 100 mg/kg/day and 500 mg/kg/day dose levels. Mean supernatant protein concentrations (mg/g liver) were statistically significant in male animals treated at 500 mg/kg/day and in female animals treated at 100 mg/kg/day and 500 mg/kg/day.

The data suggest that the test compound is acting as a relatively strong peroxisome proliferator under the conditions used in the study, as evidenced by its effects on cyanide-insensitive palmitoyl CoA oxidase activity. The effects would appear more pronounced in male animals compared to those measured in females.

Please note it is well known that measurements of the activity of acyl CoA oxidase are reliable markers of PPAR-alpha activation. Furthermore it has been shown that activation of the human form of PPAR-alpha does not result in the proliferation of hepatic cells, since this mechanism of action, which is very well responsive in rodents, is not operational with human PPAR-alpha. (Cheung et al 2004, Morimura et al., 2006, Shah et al 2007). So, it has been concluded from extensive research that these effects seen in rats and mice are not likely to be relevant to humans (Lake, 2009).

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UNITED STATES US

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CAD: 0943884/CAFE2511

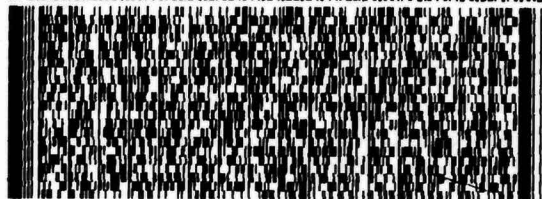
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EPA EAST - ROOM 6428 (USEPA)  
WASHINGTON DC 200043302**

(202) 564-8940

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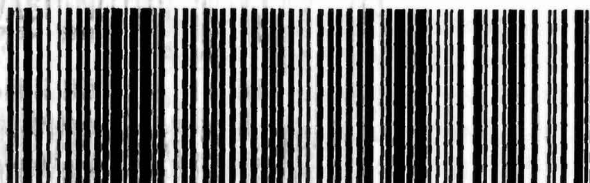
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# SOLVAY FLUORIDES

A SUBSIDIARY OF SOLVAY CHEMICALS, INC.

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Enforcement and Compliance, TSCA

**CONTAINS NO CBI**

**Re: Solvay Fluorides---TSCA Section 8(e) ---Hexafluoro-1,3 butadiene (SIFREN® 46,  
CAS # 685-63-2) --- Inhalation Administration (Whole body Exposure) to CD Rats  
for 4 weeks followed by a 2 week recovery period Toxicity Study**

To Whom It May Concern:

This letter is being submitted by Solvay Fluorides, LLC ("Solvay Fluorides") pursuant to Section 8(e) of the Toxic Substances Control Act (TSCA). Enclosed is the Toxicity Study by Inhalation Administration (Whole body Exposure) to CD Rats for 4 weeks followed by a 2 week recovery period for Hexafluoro-1,3 butadiene (SIFREN® 46, CAS # 685-63-2).

This study was performed at Huntingdon Life Sciences, Huntingdon Research Centre, Huntingdon, England, to assess the systemic toxic potential of hexafluoro-1,3 butadiene. Three groups of rats were exposed in a whole body exposure system to hexafluoro-1,3 butadiene by inhalation of study mean analyzed concentrations of 5 (Low), 15 (Mid), and 51 (High) ppm hexafluoro-1,3 butadiene in air, 6 hours a day for 4 consecutive weeks. Recovery from any effects was assessed during a 2-week recovery period.

A complete summary of the results may be found in Appendix A.

Significant adverse effects noted were as follows:

Group mean urine volume was lower than Control for all treated groups. The reduced urine volume in the High level exposure Group was associated with increased specific gravity, urinary potassium concentration and urinary chloride concentration, which were statistically significant for females.



Solvay Fluorides, LLC  
A Subsidiary of Solvay Chemicals, Inc.  
3333 Richmond Avenue, Houston, Texas 77098  
Tel: 713.525.6700 FAX: 713.525.7805  
www.solvaychemicals.us



277993

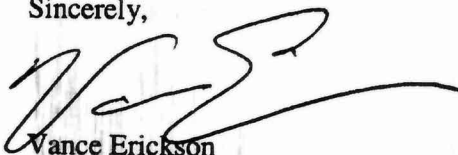
Kidney weights for test groups were greater than Control following 4 weeks of exposure and attained statistical significance for Mid and High level exposure Groups. Kidney weights of High level exposure Group female rats remained higher than Control following the 2 weeks of recovery. The changes in kidney weight are considered to be treatment-related and may be associated with changes in renal function.

The main study microscopic examination revealed treatment-related increased incidence of pseudogland formation in the respiratory epithelium and in the nasal turbinates of High level exposure Group male rats. It also revealed increased incidences of cortical tubules with hyaline droplets in the kidneys of all male treated groups, which is considered to be of no significance to man.

At the Mid and High level exposure levels, microscopic changes in the nasal turbinates and a reduced weight gain were found.

If there are any questions please feel free to contact me at 713-525-6570.

Sincerely,



Vance Erickson  
Sr. Vice President

The main study  
pseudogland  
exposure (f)

Enclosure  
man.

At the Mid and High level exposure levels, microscopic changes in the nasal turbinates and a reduced weight gain were found.

If there are any questions please feel free to contact me at 713-525-6570.

Sincerely,



Vance Erickson  
Sr. Vice President

Enclosure

## Appendix A

Summary of results from the Toxicity Study by Inhalation Administration (Whole body Exposure) to CD Rats for 4 weeks followed by a 2 week recovery period for Hexafluoro-1,3-butadiene (SIFREN® 46, CAS # 685-63-2).

There were no treatment-related clinical signs detected pre-exposure, during exposure, post exposure or during the weekly physical examination arena observations.

There were no treatment-related effects on sensory reactivity, grip strength or motor activity.

Reduced mean body weight gains were evident for rats of Mid and High level exposure Groups during the exposure periods and attained statistical significance for the High exposure Group female rats.

A slight reduction in food consumption was evident for Mid (females only) and High level (both sexes) Group rats during the exposure period. A slight reduction in food consumption was still evident for High level Group (females only) during the recovery period.

A slight reduction in water consumption was evident for female rats in the Mid and High level Groups during the exposure period. Reduced water consumption was still evident for High level Group females during the recovery period.

There were no significant abnormalities observed during pretreatment ophthalmic examination. There were no treatment-related effects noted during the examination in Week 4.

There were no treatment-related effects on hematology parameters including those examined in bone marrow.

Blood urea levels were higher than Control in all treated groups following 4 weeks of exposure and attained statistical significance for male rats of the Mid and High level exposure Groups and female rats in the High level Group. At the end of the recovery period, urea levels were similar for Control and High level exposure Groups. The elevation of the blood urea levels is considered to be likely a consequence of changes in renal functions and is considered to be of no toxicological importance due to a lack of dose-relationship.

Group mean urine volume was lower than Control for all treated groups. The reduced urine volume in the High level exposure Group was associated with increased specific gravity, urinary potassium concentration and urinary chloride concentration, which were statistically significant for females.

A dose-related increase of urinary fluoride was evident in both sexes of all test Groups following 4 weeks of exposure and attained significance for the Mid and High level exposure Groups. Urinary fluoride levels for High level exposure Group remained higher than Control following the 2 weeks of recovery and remained statistically significant.

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DKN 105/024077

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HEXAFLUORO-1,3-BUTADIENE

TOXICITY STUDY BY

INHALATION ADMINISTRATION (WHOLE BODY EXPOSURE)

TO CD RATS FOR 4 WEEKS

FOLLOWED BY A 2 WEEK RECOVERY PERIOD

**Sponsor**

Ausimont SpA.,  
Viale Lombardia 20,  
20021 Bollate,  
Milano,  
ITALY.

Daikin Industries Ltd.,  
Chemical Division,  
1-1, Nishi-Hitotsuya,  
Settsu-city,  
Osaka 566-8585,  
JAPAN.

Kanto Denka Kogyo Co., Ltd.,  
2-1 Marunouchi 1-chome,  
Chiyoda-ku, 100-0005,  
JAPAN.

Ausimont SpA.  
Viale Lombardia 20  
20021 Bollate  
Milano  
ITALY.

**Research Laboratory**

Huntingdon Life Sciences Ltd.,  
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Alconbury,  
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Cambridgeshire,  
PE28 4HS,  
ENGLAND.

Report issued: 29 May 2003

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DKN 105/024077

**COMPLIANCE WITH GOOD LABORATORY PRACTICE**  
**HEXAFLUORO-1,3-BUTADIENE**  
**TOXICITY STUDY BY**  
**INHALATION ADMINISTRATION (WHOLE BODY EXPOSURE)**  
**TO CD RATS FOR 4 WEEKS**  
**FOLLOWED BY A 2 WEEK RECOVERY PERIOD**

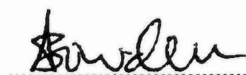
The study described in this report was conducted in compliance with the following Good Laboratory Practice standards and I consider the data generated to be valid:

The UK Good Laboratory Practice Regulations 1999 (Statutory Instrument No 3106).

OECD Principles of Good Laboratory Practice (as revised 1997), ENV/MC/CHEM(98)17.

EC Commission Directive 1999/11/EC of 8 March 1999 (Official Journal No L 77/8).

The phase performed by the Principal Investigator (Determination of urinary fluoride in rats) was conducted in compliance with the Principles of Good Laboratory Practice (GLP) as set forth in the UK GLP Regulations described above.



Anthony M. Bowden, B.Sc. (Hons.), C.I.A.T.,  
Study Director,  
Huntingdon Life Sciences Ltd.



Date

**QUALITY ASSURANCE STATEMENT**  
**HEXAFLUORO-1,3-BUTADIENE**  
**TOXICITY STUDY BY**  
**INHALATION ADMINISTRATION (WHOLE BODY EXPOSURE)**  
**TO CD RATS FOR 4 WEEKS**  
**FOLLOWED BY A 2 WEEK RECOVERY PERIOD**

The following inspections and audits have been carried out in relation to this study:

Study Phase	Date of Inspection	Date of Reporting
<b>Protocol Audit</b>	3 October 2002	3 October 2002
<b>Study Based Inspections</b>		
Study preparation )		
Exposure and generation of test atmospheres )		
Atmosphere sampling )	22 October 2002	23 October 2002
Test item control and disposition )		
Water consumption )		
Post dose observations )		
Clinical signs examinations	23 October 2002	23 October 2003
Necropsy	19 November 2002	19 November 2002
<b>Report Audit</b>	7 May 2003	8 May 2003

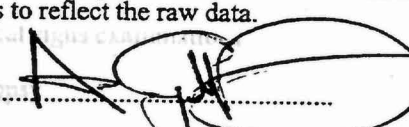
**Protocol Audit:** An audit of the protocol for this study was conducted and reported to the Study Director and Company Management as indicated above.

**Study based inspections:** Inspections of phases of this study were conducted and reported to the Study Director and Company Management as indicated above.

**Process based inspections:** At or about the time this study was in progress inspections of other routine and repetitive procedures employed on this type of study were carried out. These were promptly reported to appropriate Company Management.

**Report Audit:** This report has been audited by the Quality Assurance Department. This audit was conducted and reported to the Study Director and Company Management as indicated above.

The methods, procedures and observations were found to be accurately described and the reported results to reflect the raw data.

  
 Andrew Gilbert, M.R.C.A., H.N.C., M.I.A.T., R.An. Tech.,  
 Group Manager,  
 Department of Quality Assurance,  
 Huntingdon Life Sciences Ltd.

  
 Date

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**PRINCIPAL INVESTIGATOR**

David Riches, B.Sc. (Hons.), C.Chem, M.R.S.C.,  
Butterworth Laboratories Ltd.

## SUMMARY

The systemic toxic potential of the test substance, Hexafluoro-1,3-butadiene to Crl:CD® (SD) IGS BR rats by inhalation administration was assessed over a period of 4 weeks, followed by a 2-week recovery period. Three groups of 5 male and 5 female rats were exposed in a whole body exposure system to Hexafluoro-1,3-butadiene by inhalation at target concentrations of 5, 15 and 50 ppm, 6 hours a day for 4 consecutive weeks. A similarly constituted Control group was exposed to clean air only. A further 5 male and 5 female rats were assigned to each of the Control and High dose groups for a 2-week recovery period following the 4-week treatment period.

During the study, clinical condition, detailed physical examination and arena observations, sensory reactivity, grip strength, motor activity, bodyweight, food consumption, water consumption, ophthalmic examination, haematology (peripheral blood and bone marrow), blood chemistry, urinalysis, urinary fluoride, organ weight, macroscopic and microscopic pathology investigations were undertaken.

Principal findings are summarised below:

### Results

The study mean analysed chamber concentrations of Hexafluoro-1,3-butadiene were 5, 15 and 51 ppm for the Low, Intermediate and High dose groups respectively. These concentrations are equivalent to 0.033, 0.099 and 0.338 mg/L (at 25°C and 760 mmHg) for Groups 2 to 4, respectively.

There was one unscheduled death. A Group 4 main study female rat was sacrificed on humane grounds following exposure on Day 14 of the study due to a suspected broken bone.

There were no treatment-related clinical signs detected pre-exposure, during exposure, post exposure or during the weekly physical examination and arena observations.

There were no treatment-related effects on sensory reactivity, grip strength or motor activity.

Reduced mean bodyweight gains were evident for rats of Groups 3 and 4 during the exposure period and attained statistical significance for Group 4 female rats.

A slight reduction in food consumption was evident for Group 3 (females only) and Group 4 (both sexes) rats during the exposure period. A slight reduction in food consumption was still evident for Group 4 female rats during the recovery period.

A slight reduction in water consumption was evident for females rats of Groups 3 and 4 during the exposure period. Reduced water consumption was still evident for Group 4 female rats during the recovery period.

There were no significant abnormalities observed during the pre-treatment ophthalmic examination. There were no treatment-related effects noted during the examination in Week 4.

There were no treatment-related effects on haematology parameters including those examined in bone marrow.

Blood urea levels were higher than control in all treated groups following 4 weeks of exposure and attained statistical significance for male rats of Groups 3 and 4 and female rats of Group 4. At the end of the recovery period urea levels were similar for Groups 1 and 4. The elevation of blood urea levels is considered likely to be a consequence of changes in renal function and is considered to be of no toxicological importance due to the lack of a dose-relationship.

Group mean urine volume was lower than control for all treated groups. The reduced urine volume in Group 4 rats was associated with increased specific gravity, urinary potassium concentration and urinary chloride concentration, which were statistically significant for females.

A dose-related increase in urinary fluoride was evident in both sexes of all test groups following 4 weeks of exposure and attained statistical significance for Groups 3 and 4. Urinary fluoride levels for Group 4 rats remained higher than controls following 2 weeks of recovery and remained statistically significant. The presence of fluoride ion in the urine is commonly associated with the metabolic breakdown of fluoride-containing compounds such as Hexafluoro-1,3-butadiene.

Kidney and liver weights for test groups were greater than controls following 4 weeks of exposure and attained statistical significance for Groups 3 and 4. Kidney weights of Group 4 female rats remained higher than controls following 2 weeks of recovery. The changes in kidney weight are considered to be treatment-related and may be associated with changes in renal function. In the absence of microscopic findings, it is considered that the increase in liver weight is of no toxicological importance.

The macroscopic examination performed at termination revealed no treatment-related abnormalities.

The main study microscopic examination revealed treatment-related increased incidence of pseudogland formation in the respiratory epithelium in the nasal turbinates of Group 4 male rats and increased incidences of cortical tubules with hyaline droplets in the kidneys of all male treated groups.

The recovery microscopic examination revealed recovery to control level for pseudogland formation in the nasal turbinates of the respiratory epithelium. Almost complete recovery had occurred for cortical tubules with hyaline droplets of the kidney.

### Conclusion

The only effects seen in rats exposed at 5 ppm were a slight increase in hyaline droplet formation in the cortical tubules of the kidney (males only) and an increase in urinary fluoride (males and females). The former is considered to be of no significance to man and the latter is a consequence of the metabolic breakdown of the test substance.

At 15 ppm and 51 ppm the adverse effects included microscopic changes in the nasal turbinates and a reduced weight gain.

The no adverse effect level, for male and females rats, is therefore considered to be 5 ppm.

### Conclusion

## INTRODUCTION

### Objective

The objective of this study was to assess the systemic toxic potential of Hexafluoro-1,3-butadiene to rats by repeat administration by inhalation, in whole body chambers for 4 consecutive weeks. Recovery from any effects was assessed during a 2-week recovery period.

### Regulatory compliance

The study was designed to meet the requirements of:

Ministry of Health and Welfare for Japan.

Organisation for Economic Co-operation and Development: Testing of Chemicals, Guideline 412

The study was conducted in accordance with the requirements of current, internationally recognised Good Laboratory Practice Standards, and the applicable sections of the United Kingdom Animals (Scientific Procedures) Act 1986.

### Test system

The rat was chosen as the test species because of its acceptance as a predictor of toxic change in man and the requirement for a rodent species by regulatory agencies. The CrI:CD<sup>®</sup> (SD) IGS BR strain was used because of the historical control data available in this laboratory.

### Route of administration

The inhalation route of administration was chosen to stimulate the conditions of potential human exposure.

### Treatment groups and dosages

The target exposure levels used in this study (0, 5, 15 and 50 ppm) were selected in conjunction with the Sponsor with reference to previous work with this compound performed in these laboratories. (Huntingdon Life Sciences Report Number: DKN 104/023513). In that study rats were exposed to target concentrations of 10, 30 and 100 ppm, where clinical effects were seen at the higher exposure levels.

### Study location

The test system was maintained at the following laboratory:

Huntingdon Life Sciences Ltd.,  
Huntingdon Research Centre,  
Woolley Road,  
Alconbury,  
Huntingdon,  
Cambridgeshire,  
PE28 4HS,  
England.

The analyses described in the inhalation administration, haematology (peripheral blood), blood chemistry, urinalysis and pathology sections of this report were performed by:

Huntingdon Life Sciences Ltd.,  
Huntingdon Research Centre,  
Woolley Road,  
Alconbury,  
Huntingdon,  
Cambridgeshire,  
PE28 4HS,  
England.

The analyses described in the haematology (bone marrow) and histology section of this report were performed by:

Huntingdon Life Sciences Ltd.,  
Eye Research Centre,  
Suffolk,  
IP23 7PX,  
England.

The analyses described in the urinary fluoride section of this report were performed by:

Butterworth Laboratories Ltd.,  
54-56 Waldegrave Road,  
Teddington,  
Middlesex,  
TW11 8NY,  
England.

The analyses described in this report were performed by:

Huntingdon Life Sciences Ltd.,  
Eye Research Centre,  
Suffolk,  
IP23 7PX,  
England.

The analyses described in this report were performed by:

Butterworth Laboratories Ltd.,  
54-56 Waldegrave Road,  
Teddington,  
Middlesex,  
TW11 8NY,  
England.

## EXPERIMENTAL PROCEDURE

### STUDY SCHEDULE AND STRUCTURE

#### Duration of treatment

The test substance, Hexafluoro-1,3-butadiene, was administered over a period of 4 consecutive weeks. Each necropsy procedure (main study and recovery study) was completed in 1 day. The duration of treatment is reported as 4 weeks. Animals assigned to the recovery phase completed a further 2 weeks without treatment.

#### Time schedule

Study initiation: (Protocol signed by Study Director)	1 October 2002
Experimental start date: (Animal arrival):	9 October 2002
Treatment commenced:	22 October 2002
Necropsy completed:	
Main Study	19 November 2002
Recovery Study	3 December 2002
Experimental completion date: (Pathology)	13 March 2003
Study completion:	29 May 2003

#### Identity of treatment groups

The study consisted of one Control and three treated groups of rats, identified as follows:

Group	Treatment	Target exposure level (ppm)	Main study (4 weeks)					
			No. of animals		Animal numbers		Cage numbers	
			Male	Female	Male	Female	Male	Female
1	Control	0	5	5	11-15	51-55	3	11
2	Hexafluoro-1,3-butadiene	5	5	5	6-10	41-45	2	9
3	Hexafluoro-1,3-butadiene	15	5	5	26-30	56-60	6	12
4	Hexafluoro-1,3-butadiene	50	5	5	16-20	36-40	4	8

Group	Treatment	Target exposure level (ppm)	Recovery phase (4 weeks + 2 weeks recovery)					
			No. of animals		Animal numbers		Cage numbers	
			Male	Female	Male	Female	Male	Female
1	Control	0	5	5	21-25	31-35	5	7
4	Hexafluoro-1,3-butadiene	50	5	5	1-5	46-50	1	10

Some serial observations needed to be performed without the knowledge of the treatment group, therefore the animal numbering system was such that it was not easy to identify a treatment group from the animal number.

## TEST SUBSTANCE

### Test substance

Information supplied by the Sponsor regarding the test substance is contained in the test substance data sheet, which is retained in study records, and the Certificate of Analysis, which is appended to this report.

The following information is given in summary:

Identification:	Hexafluoro-1,3-butadiene
Description:	Colourless, liquified gas (under pressure)
Storage conditions:	At ambient room temperature (ca. 20°C) and in the original container
Supplier:	Sponsor
Batch number:	031070P
Date of receipt:	22 April 2002
Quantity received:	6 x 3.0 kg
Expiry:	2007
Purity:	99.8%

The Sponsor was responsible for the characterisation of the test substance and the documentation of the methods of synthesis, fabrication or derivation and stability.

It was not practical for a small sample to be taken and stored in Archives since the test substance was contained in a pressurised cylinder.

## ANIMAL MANAGEMENT

### Animal supply, acclimatisation and allocation

A total of 33 male and 33 female Crl:CD® (SD) IGS BR rats were received from Charles River (UK) Ltd, Margate, Kent, England. The rats were ordered at 42 to 49 days of age and within a weight range of 11 g for each sex.

On arrival, the animals were removed from the transit boxes and allocated to study cages. Using the sequence of cages in the battery, one animal at a time was placed in each cage with the procedure being repeated until each cage held the appropriate number of animals. Each sex was allocated separately.

Each animal was assigned a number and uniquely identified within the study by a tail tattoo. Each cage label was colour-coded according to group and was uniquely numbered with cage and study number, as well as the identity of the occupants.

Before the start of treatment, one female with non-resolving ophthalmic lesions was replaced with a spare animal of suitable weight from the same batch.

The animals were allowed to acclimatise to the conditions described below for 13 days before treatment commenced. For those animals selected for this study, their age at the start of treatment was 55 to 62 days and their bodyweights were in the range of 271 to 320 g for males and 207 to 260 g for females.

The spare animals were removed from the study room after treatment commenced.

#### **Animal housing, diet and water supply**

Animals were housed inside a restricted entry rodent facility (Building Y14, Room 011). The facility was designed and operated to minimise the entry of external biological and chemical agents and to minimise the transference of such agents between rooms. Before the study the room was cleaned.

Each animal room was kept at positive pressure with respect to the outside by its own supply of filtered fresh air, which was passed to atmosphere and not re-circulated. Temperature and relative humidity were monitored continuously. The temperature and relative humidity controls were set to be generally maintained, where possible, within the range of 19 to 23°C and 40 to 70%, respectively. Recorded ranges were 19 to 22.5°C for temperature and 31 to 52% for relative humidity. Deviations outside these ranges were considered to have no adverse effects on the condition of the animals. Artificial lighting was controlled to give a cycle of 12 hours continuous light and 12 hours continuous dark per 24 hours.

Alarms were activated if there was any failure of the ventilation system, or temperature limits were exceeded. A stand-by electricity supply was available to be automatically brought into operation should the public supply fail.

The animals were housed five of one sex per cage. The cages (North Kent Plastic; dimensions 35 cm x 53 cm x 25 cm) were made of a stainless steel body with a stainless steel grid floor, and were suspended on aluminium racks, above absorbent paper which was changed at appropriate intervals. Cages, cage-trays, food hoppers and water bottles were changed at appropriate intervals.

The animals were allowed free access to a standard rodent diet (Rat and Mouse No. 1 Maintenance Diet from Special Diets Services Ltd., Witham, Essex, England), except during the 6 hour exposure or when urine was being collected and overnight before routine blood sampling. This diet contained no added antibiotic or other chemotherapeutic or prophylactic agent.

Water taken from the public supply was freely available via polycarbonate bottles fitted with sipper tubes, except when urine was being collected.

Each batch of diet was analysed routinely by the supplier for various nutritional components and chemical and microbiological contaminants. Supplier's analytical certificates were scrutinised and approved before any batch of diet was released for use. The quality of the water supply is governed by regulations published by the Department for Environment, Food and Rural Affairs (formerly known as the Department of the Environment). Certificates of analysis were received routinely from the supplier. Since the results of these various analyses did not provide evidence of contamination that might have prejudiced the study, they are not presented.

No other specific contaminants that were likely to have been present in the diet or water were analysed, as none that may have interfered with or prejudiced the outcome of the study was known.

### **Administration**

The vaporous test substance was administered for 6 hours a day, for 4 consecutive weeks.

The rats were exposed to the test atmosphere in whole body exposure chambers constructed from stainless steel and glass, with an internal volume of 0.75 m<sup>3</sup>. The test atmosphere was produced by metering the test liquid from a stainless steel pressure resistant cylinder, followed by dilution with clean air prior to the resultant vapour atmosphere passing into the exposure chamber.

The target concentrations for exposure were 5 ppm (Low dose), 15 ppm (Intermediate dose) and 50 ppm (High dose).

Details of administration and analysis of the test atmospheres together with results obtained are presented in **ADMINISTRATION OF HEXAFLUORO-1,3-BUTADIENE BY INHALATION TO RATS** appended to this report.

### **SERIAL OBSERVATIONS**

Dated and signed records of all activities relating to the day by day running and maintenance of the study within the animal unit as well as to the group observations and examinations outlined in this procedure were recorded in the Study Day Book. In addition, observations relating to individual animals made throughout the day were recorded.

All observations described below were performed in cage number sequence except where otherwise indicated.

### **Clinical observations**

Animals were inspected visually at least twice daily for evidence of ill-health or reaction to treatment. Cages and cage-trays were inspected daily for evidence of ill-health amongst the occupants, such as loose faeces. Any deviation from normal was recorded at the time in respect of nature and severity, date and time of onset, duration and progress of the observed condition, as appropriate.

In addition, detailed observations were recorded daily, on the days of exposure as follows:

#### **Pre-exposure observation**

During exposure (recorded as a group response as not all animals observable)

As each animal is returned to its home cage

As late as possible in the working day.

In addition, a more detailed weekly physical examination was performed on each animal to monitor general health.

During the acclimatisation and recovery periods, observations of the animals and their cages were recorded at least once per day.

#### **Detailed physical examination and arena observations**

Before treatment commenced and during each week of treatment and Week 2 of the recovery period, a detailed physical examination and arena observations were performed on each animal. On each occasion, the examinations were performed at approximately the same time of day (before exposure during the treatment period), by an observer unaware of the experimental group to which the animal belonged.

After removal from the home cage, animals were assessed for physical condition and behaviour during handling and after being placed in a standard arena. Any deviation from normal was recorded with respect to the nature and, where appropriate, degree of severity. Particular attention was paid to possible signs of neurotoxicity such as convulsions, tremors and abnormalities of gait or behaviour. Attention was also given to the detection of audible respiratory noise.

Findings were either reported as "present" or assigned a severity grade - slight, moderate or marked.

#### **Neurobehavioural screening**

During Week 4 of treatment, sensory reactivity, grip strength and motor activity assessments were performed. A grip strength assessment was also performed during Week 2 of recovery. Animals were not necessarily all tested on the same day, but the number of animals was balanced across the groups on each day of testing. These procedures were performed prior to any laboratory investigations and before exposure.

Each animal was subjected to the procedures detailed below, on the specified occasions, by an observer who was unaware of the treatment group to which each animal belonged. Before the start of each set of observations, cage labels showing the treatment groups were replaced by labels stating only the study, animal and cage numbers.

Sensory reactivity and grip strength assessments were performed in Y14, Room 011 and the motor activity assessment was performed in Y14, Room 008.

#### **Sensory reactivity**

The following reflexes and responses were recorded:

**Approach response** - A blunt probe was brought towards the animal's head until it was close to the animal's nose (but not touching the vibrissae). The animal's reaction was recorded as: 1 - no reaction or ignores probe; 2 - normal awareness and reaction (approaches and/or sniffs probe); or 3 - abnormally fearful or aggressive reaction.

**Touch response** - The animal's flank was stroked gently with a blunt probe and the reaction recorded as: 1 - no reaction or ignores probe; 2 - normal awareness and reaction (turns towards or moves away); 3 - abnormally fearful or aggressive reaction.

**Auditory startle reflex** - The animal's response to a sudden loud noise was assessed. The animal was stationary and the source of sound was not visible. The response was scored as: 1 - no response; 2 - weak response (ear twitch only); 3 - normal response (obvious flinch or startle); or 4 - exaggerated response (all feet off the floor).

**Tail pinch response** - The animal's tail was pinched sharply with forceps approximately one third from the tip. The response was graded as: 1 - no response; 2 - weak response (turns round slowly or weak vocalisation without moving away); 3 - normal response (jumps forward or turns around sharply, usually with vocalisation); 4 - exaggerated response (excessive vocalisation, body movement or aggression).

At any point during the observations, where considered appropriate, additional comments were made as free text. As no treatment-related changes were observed, the examination was not performed during the recovery phase.

### **Grip strength**

Forelimb and hindlimb grip strength was measured using a Mecmesin Portable Force Indicators. Two trials were performed. As apparent treatment-related changes were observed, the examination was performed during the recovery phase.

At any point during the examinations, where considered appropriate, additional commitments were made as free text.

### **Motor activity**

Motor activity was recorded using a Coulbourn Infra-Red Activity Monitoring System (Coulbourn Instruments, 7462 Penn Dr, Allentown, PA 18106, USA), an automated system.

This system uses infra-red detectors to monitor activity. The following categories of activity are recorded: the time spent in locomotor activity, non-locomotor activity and in no movement. The number of occurrences (events) of each category is also recorded. For reporting purposes, only the time spent in locomotor activity is presented routinely.

For testing, each animal was placed singly into a clear polycarbonate observation cages with eight infra-red beams (four high and four low). The test session for each animal was 1 hour, with data collected every 2 minutes.

As no treatment-related changes were observed, the examination was not performed during the recovery phase.

### **Mortality**

Debilitated animals were observed carefully and, where necessary, isolated to prevent cannibalism. Animals judged *in extremis* were killed. Animals were also killed to prevent unnecessary or prolonged suffering. Where possible, blood samples were taken *ante mortem* and analysed for the characteristics specified in the haematology and blood chemistry sections below. A complete necropsy was performed in all cases as described below

**Bodyweight**

The weight of each rat was recorded one week before treatment commenced (Week -1), on the day that treatment commenced (Day 0), weekly throughout the treatment and recovery periods, and before necropsy.

**Food consumption**

The weight of food supplied to each cage, that remaining and an estimate of any spilled was recorded for the week before treatment started (Week -1), and each week throughout the treatment and recovery periods. From these records the mean weekly consumption per animal (g/animal) was calculated for each cage.

**Water consumption**

The quantity of water consumed by each cage of rats was recorded daily, commencing 1 week prior to the start of exposures and throughout the treatment and recovery periods, using water bottles fitted with sipper tubes.

**Ophthalmic examination**

Before treatment commenced, the eyes of all animals allocated to the study (including spare animals) were examined by means of a binocular indirect ophthalmoscope. Rejected animals were replaced with animals with no adverse ocular abnormality, selected from the spare animals for the study. During Week 4 of treatment the eyes of all animals of Groups 1 (Control) and 4 (High dose) were similarly examined.

Prior to each examination, the pupils of each animal were dilated using 0.5% tropicamide ophthalmic solution (Mydriacyl, Alcon Laboratories Ltd.). The adnexae, conjunctiva, cornea, sclera, anterior chamber, iris (pupil dilated), lens, vitreous and fundus were examined.

As no treatment-related changes were observed, the examination was not performed during the recovery phase or for animals of Groups 2 or 3 (Low or Intermediate dose).

**Haematology, peripheral blood**

Immediately prior to sacrifice following the last day of exposure and the last day of the recovery period, blood samples were obtained from all animals after overnight starvation. Animals were held under light general anaesthesia induced by isoflurane and blood samples were withdrawn from the retro-orbital sinus.

Blood samples (nominally 0.5 ml) were collected into EDTA as anticoagulant and examined for the characteristics described below.

The following were measured using a Bayer-Technicon H1E haematology analyser:

- Haematocrit (Hct)
- Haemoglobin (Hb)
- Red blood cell count (RBC)
- Mean cell haemoglobin (MCH)
- Mean cell haemoglobin concentration (MCHC)
- Mean cell volume (MCV)
- Total white cell count (WBC)
- Differential WBC count
  - Neutrophils (N)
  - Lymphocytes (L)
  - Eosinophils (E)
  - Basophils (B)
  - Monocytes (M)
  - Large unstained cells (LUC)
- Platelet count (Plt)

Reticulocyte count (Retic) - using a Sysmex R3000 Reticulocyte Counter.

Blood film - examined using a Bayer-Technicon H1E haematology analyser for abnormal morphology and unusual cell types, including normoblasts. The most common morphological changes, anisocytosis, micro/macrocytosis, hypo/hyperchromasia were recorded as follows:

-	=	no abnormalities detected
+	=	slight

Additional blood samples (nominally 0.5 ml) were taken into citrate anticoagulant and examined in respect of:

Prothrombin time (PT) using an ACL 3000 Plus analyser and IL PT-Fibrinogen reagent - method of Quick, A.J., (1942).

Activated partial thromboplastin time (APTT) using an ACL 3000 Plus Analyser and IL APTT reagent - method of Proctor, R.R. and Rapaport, S.I., (1961).

Abbreviations in parenthesis used in Table 8 and Appendix 8.

### Haematology, bone marrow

Bone marrow samples were obtained from the tibia during necropsy of all animals killed. Smears prepared from these samples were air-dried, fixed in methanol and stained using a Romanowsky procedure.

The smears from all animals sacrificed on completion of the scheduled treatment and recovery period were examined to assess the cellularity (Cellular), distribution (Distrib) of cell types and cell morphology (Morp) of the bone marrow.

Abbreviations in parenthesis used in Appendix 9.

### Blood chemistry

At the same time and using the same animals as for peripheral blood haematology, further blood samples (nominally 0.7 ml) were collected into lithium heparin as anticoagulant. All tubes were mechanically agitated and the sample subsequently centrifuged in order to separate the plasma.

After separation, the plasma was examined using a Hitachi 917 Clinical Chemistry Analyser in respect of:

- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma-glutamyl transpeptidase (gGT)
- Creatine phosphokinase (CPK Total)
- Total Bilirubin (Bili)
- Urea
- Creatinine (Creat)
- Glucose (Gluc)
- Total cholesterol (Chol)
- Triglycerides (Trig)
- Sodium (Na)
- Potassium (K)
- Chloride (Cl)
- Calcium (Ca)
- Inorganic phosphorus (Phos)
- Total protein (Total Prot)

Electrophoretic protein fractions; albumin (Alb),  $\alpha$ 1 globulin ( $\alpha$ 1),  $\alpha$ 2 globulin ( $\alpha$ 2),  $\beta$  globulin (Beta),  $\gamma$  globulin (Gamma) were analysed with agarose gel, using a Beckman test kit, staining with Ponceau-S and scanning with a suitable densitometer.

Albumin/globulin ratio (A/G Ratio) was calculated from total protein concentration and analysed albumin concentration.

Abbreviations in parenthesis used in Table 9 and Appendix 10.



United States Environmental Protection Agency  
Washington, DC 20460

ML55779



## Permanent Transfer Receipt for TSCA Confidential Business Information

I acknowledge receipt of the following documents containing  
TSCA Confidential Business Information.

*For: John Gorman*

1. DCN/Copy Number <i>0001</i>	Description <i>Letter, TSCA 8(e) Submission</i>
2. DCN/Copy Number	Description
3. DCN/Copy Number	Description
4. DCN/Copy Number	Description
5. DCN/Copy Number	Description
6. DCN/Copy Number	Description
7. DCN/Copy Number	Description
8. DCN/Copy Number	Description

Date of transfer <i>4-21-16</i>	Name of Sending DCO/DCA <i>Gloria Davis</i> <b>GLORIA DAVIS</b>
------------------------------------	--

Name of Recipient <i>Mark Bean</i>	Signature of Recipient DCO/DCA <i>[Signature]</i> <b>4/26/2016</b>
---------------------------------------	---

### INSTRUCTIONS

CONFIDENTIALITY CLAIM  
WITHDRAWN 4/21/2016

1. To be used only for permanent transfer of TSCA CBI. Transfers must be made by a *see attached* DCO/DCA.

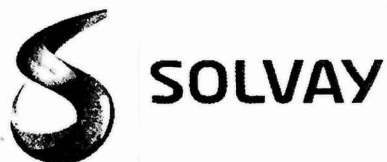
2. The sending DCO/DCA must keep the original of this form after it has been signed and returned by the recipient DCO/DCA. The Recipient DCO/DCA must keep a copy of the receipt after returning the original to the sending DCO/DCA.



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**VIA FEDEX**

March 24, 2016

TSCA Confidential Business Information Center (7407M)  
WJC East - Room 6428  
Attn: Section 8(e)  
U.S. Environmental Protection Agency  
1201 Constitution Avenue, N.W.  
Washington, D.C. 20004-3302

**CONFIDENTIAL**  
This submission is entirely  
confidential and cannot be made non-  
confidential by redaction

**Re: TSCA 8(e) Submission; Chemical Abstract Services Registry Numbers  
("CASRN") 375-95-1, 335-67-1, 1763-23-1, 335-76-2, 2058-94-8, and 355-46-4**

Dear Sir/Madam:

Solvay Specialty Polymers USA, LLC (Solvay) is making this submission to the U.S. Environmental Protection Agency (EPA) pursuant to Section 8(e) of the Toxic Substances Control Act ("TSCA", 15 U.S.C. § 2601 *et seq.*). Solvay recently became aware of certain human serum sampling results. These data confirm the well-known fact that a number of perfluorinated chemicals ("PFCs") have become widely dispersed in the environment to the extent that very low levels are present in essentially all human serum. The current data reveal that perfluorononanoic acid ("PFNA", CASRN 375-95-1) is present at levels over the national average in the serum of a small group tested. PFNA was previously used at Solvay's West Deptford, New Jersey, facility; the serum samples have been reported to Solvay as being from residents that obtained their drinking water from private wells in West Deptford Township. These data were provided to Solvay by another party in a context that imposes limits on Solvay's use of this information. Accordingly, Solvay is obligated to assert confidentiality regarding this entire submission.

Solvay has received only limited information on the individuals tested. Solvay had no role in the selection of the individuals tested or the testing methodology employed. The results of this investigation are only applicable to the individuals tested. The results cannot be generalized to other populations and appear to represent data from two clusters that had distinctly different sources of exposure; whether the exposure of either or both is representative of the local environment is unknown. In addition, these results cannot be used to predict the future occurrence of disease or be associated with current or past health problems. Also, serum PFC concentrations do not provide information about the source of exposure (*i.e.*, water, soil, or food) or how the tested individuals vary with regard to their interactions with different potential exposure pathways.

March 24, 2016

Page 2

Solvay is reporting these human serum data pursuant to section 8(e) of TSCA despite the fact that Solvay ceased use of PFNA in 2010 and believes it no longer has any obligation under TSCA section 8(e) for PFNA. These data are being submitted based solely on a 2006 EPA guidance document on TSCA section 8(e) reporting that "If the new information on a chemical known to have serious toxic effects indicates a level of exposure previously unknown to the Administrator, it should be reported. Information that corroborates known exposure levels, such as those within the range of chemical blood levels and other biological monitoring data recorded in the [CDC] NHANES (National Health and Nutrition Examination Survey) data base, is not reportable."<sup>1</sup> Consequently, it appears that EPA considers any serum sampling data in excess of the levels reported in the NHANES database as evidence of substantial risk even if those levels, while above the national background, are still so low as to not actually pose a substantial risk. For PFNA, the February 2015 Tables from CDC's *Fourth National Report on Human Exposure to Environmental Chemicals* show a geometric mean of 0.881 µg/L for the latest survey period, 2011-2012.<sup>2</sup>

The serum data obtained by Solvay represent only seven individuals. The PFNA result for each individual in the group exceeds the geometric mean of 0.881 µg/L for the 2011-2012 NHANES survey period. The serum data also include test results for perfluorooctanoic acid (PFOA, CASRN 335-67-1), perfluorooctane sulfonic acid (PFOS, CASRN 1763-23-1), perfluorodecanoic acid (PFDA, CASRN 335-76-2), perfluoroundecanoic acid (PFUnA, CASRN 2058-94-8), and perfluorohexane sulfonic acid (PFHxS, CASRN 355-46-4). Each of the seven individuals has levels in excess of the NHANES mean for at least two of the other five PFCs, as shown by the enclosed table.

Actions taken by Solvay, including the submission of this report, should not be taken to mean that Solvay recognizes or admits there is any health issue with respect to the presence of PFNA or other PFCs in human serum at the detected levels or that Solvay is in any way responsible for these substances if they are found; other sources have contributed to ambient PFC levels in the environment.

If you have any questions or require additional information regarding this submission, please do not hesitate to contact me.

Sincerely,



Charles Jones  
Plant Manager  
Solvay Specialty Polymers USA, LLC

Enclosures

<sup>1</sup> EPA, "Toxic Substances Control Act (TSCA) Section 8(e) Substantial Risk Notifications-Frequent Questions" (Sept. 2006) (Q & A 2), available at <http://www.epa.gov/oppt/tsca8e/pubs/frequentlyaskedquestionsfaqs.html>.

<sup>2</sup> CDC, "Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables" (Feb. 2015), available at [http://www.cdc.gov/biomonitoring/pdf/FourthReport\\_UpdatedTables\\_Feb2015.pdf](http://www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Feb2015.pdf).

CONFIDENTIAL

This submission is entirely confidential and cannot be made non-confidential by redaction

Sample	PFNA (ug/L)	PFOA (ug/L)	PFOS (ug/L)	PFDA (ug/L)	PFUnA (ug/L)	PFHxS (ug/L)
Individual 1	35	29.7	13.6	U 0.5	U 0.5	2.09
Individual 2	55.8	60.8	9.04	U 0.5	U 0.5	3.5
Individual 3	11.5	13.7	2.9	U 0.5	U 0.5	U 1
Individual 4	2.26	2.16	6.69	U 0.5	U 0.5	U 1
Individual 5	7.63	2.31	78.2	2.78	3.58	1.78
Individual 6	5.01	1.61	28	0.812	1.81	1.01
Individual 7	2.05	1.3	9.03	U 0.5	0.898	U 1
NHANES Geometric Mean 2009-2010	1.26	3.07	9.32	0.279	0.172	1.66
NHANES Geometric Mean 2011-2012	0.881	2.08	6.31	0.199	--	1.28

**Bold** values exceed the NHANES geometric mean for the 2011-2012 survey period (2009-2010 for PFUnA, which did not have a 2011-2012 NHANES calculation)

"U" indicates value below the method quantitation limit

## **TSCA 8(e) Substantiation of Confidentiality**

- (1) Is your company asserting this confidential business information (CBI) claim on its own behalf? If the answer is no, please provide company name, address and telephone number of entity asserting claim.*

On its own behalf, Solvay Specialty Polymers USA, LLC ("Solvay") provides the following substantiation of its claims to hold confidential this submission under section 8(e) of the Toxic Substances Control Act (TSCA) (15 U.S.C. § 2607(e)).

- (2) For what period do you assert your claim(s) of confidentiality? If the claim is to extend until a certain event or point in time, please indicate that event or time period. Explain why such information should remain confidential until such point.*

The confidentiality of the information being submitted arises from the circumstances which allowed Solvay to gain access to these data at this time. Solvay obtained these data on the condition that there would be no distribution and use beyond Solvay. It is anticipated that the owner of the data will make the data public in the future or the limitations on Solvay's ability to release the data will be lifted. Solvay is not in control of when this will occur, but can commit to tell EPA when the restrictions associated with this data have been lifted.

- (3) Has the information that you are claiming as confidential been disclosed to any other governmental agency, or to this Agency at any other time? Identify the Agency to which the information was disclosed and provide the date and circumstances of the same. Was the disclosure accompanied by a claim of confidentiality? If yes, attach a copy of said document reflecting the confidentiality agreement.*

Solvay has only recently obtained this confidential information and therefore has never disclosed this information in any filing with EPA or other government agencies, nor has Solvay disclosed the information as part of a health and safety study to any other Federal agency.

- (4) Briefly describe any physical or procedural restrictions within your company relating to the use and storage of the information you are claiming CBI.*

Distribution of this confidential information has been restricted to only those employees and outside counsel with a need to know. Employees are under a duty to protect the confidentiality of this information. As a general matter, Solvay requires that such employees sign an agreement prohibiting disclosure of confidential information to prevent undesired disclosure by employees who leave the Company.

- (5) *If anyone outside your company has access to any of the information claimed CBI, are they restricted by confidentiality agreement(s). If so, explain the content of the agreement(s).*

This information has been held strictly confidential and has not been disclosed to persons outside of Solvay, except as part of confidential and privileged communications with outside legal counsel and under non-disclosure agreements with third parties when such parties need to know such information. Future disclosures will be similarly restricted. Further, only those employees within Solvay with a need-to-know obtain this information.

- (6) *Does the information claimed as confidential appear or is it referred to in any of the following: a) advertising or promotional material for the chemical substance or the resulting end product; b) material safety data sheets or other similar materials (such as technical data sheets) for the substance or resulting end product (include copies of this information as it appears when accompanying the substance and/or product at the time of transfer or sale); c) professional or trade publications; or d) any other media or publications available to the public or to your competitors. If you answered yes to any of the above, indicate where the information appears, include copies, and explain why it should nonetheless be treated as confidential.*

The information claimed as confidential does not appear in advertising or promotional materials, safety data sheets or other similar materials, professional or trade publications, or any other media available to the public or competitors.

- (7) *Has EPA, another federal agency, or court made any confidentiality determination regarding information associated with this substance? If so, provide copies of such determinations.*

To the best of Solvay's knowledge, no Federal agency or court has ruled on the confidentiality of this information.

- (8) *Describe the substantial harmful effects that would result to your competitive position if the CBI information is made available to the public? In your answer, explain the causal relationship between disclosure and any resulting substantial harmful effects. Consider in your answer such constraints as capital and marketing cost, specialized technical expertise, or unusual processes and your competitors' access to your customers. Address each piece of information claimed CBI separately.*

Disclosure of the information claimed as confidential is likely to irreparably impair Solvay's ability to acquire additional relevant data from the owner of these data in a timely manner. It could also result in sanctions being imposed on Solvay.

- (9) *Has the substance been patented in the U.S. or elsewhere? Is a patent for the substance currently pending?*

Solvay knows of no pending patents for the substances discussed in the section 8(e) submission.

- (10) *Is this substance/product commercially available and if so, for how long has it been available on the commercial market? If on the commercial market, are your competitors aware that the substance is commercially available in the U.S.? If not already commercially available, describe what stage of research and development (R&D) the substance is in, and estimate how soon a market will be established. What is the substance used for and what type of product(s) does it appear in?*

As noted below, the perfluorinated chemicals (PFCs) that are the subject of this submission all have Chemical Abstract Services Registry Numbers (CASRNs) and were/are commercially available in U.S. commerce. As noted above, Solvay's confidentiality obligations associated with these data arise from the manner by which the data were obtained and not because the substance involved is unknown in commerce.

- (11) *Describe whether a competitor could employ reverse engineering to identically recreate the substance.*

As noted in the response above, confidentiality does not arise from the identity of the substance.

- (12) *Do you assert that disclosure of this information you are claiming CBI would reveal: a) confidential processes used in manufacturing the substance; b) if a mixture, the actual portions of the substance in the mixture; or c) information unrelated to the effects of the substance on human health or the environment? If your answer to any of the above questions is yes, explain how such information would be revealed.*

The substances identified are not mixtures and the confidentiality of the information does not arise from use of a confidential process. Disclosure of the information, *per se*, is what is confidential without regard to the effects of the substance on human health or the environment.

- (13) *Provide the Chemical Abstract Service Registry Number for the product, if known. Is your company applying for a CAS number now or in the near future? If you have applied for a CAS number, include a copy of the contract with CAS.*

CASRNs exist for all the PFCs for which the Centers for Disease Control and Prevention's (CDC) National Health and Nutrition Examination Survey (NHANES) publishes blood level data. The CASRNs for these substances are identified in the text of the notification and will be available for disclosure once Solvay is able to publically acknowledge its receipt of these data.

Substantiation of Confidentiality for March 2016 TSCA 8(e) Submission by Solvay Specialty Polymers, USA LLC – Contains Confidential Information

- (14) *Is the substance or any information claimed CBI the subject of FIFRA regulation or reporting? If so, explain.*

No.

**CONFIDENTIAL**  
This submission is entirely confidential  
and cannot be made non-confidential by  
redaction

ORIGIN ID:DYLA (856) 251-3404  
KATHLEEN MEEHAN  
SOLVAY SOLEXIS, INC.  
10 LEONARD LANE

WEST DEPTFORD, NJ 08086  
UNITED STATES US

SHIP DATE: 24MAR16  
ACTWGT: 0.2 LB MAN  
CAD: 0943884/CAFE2912

BILL SENDER

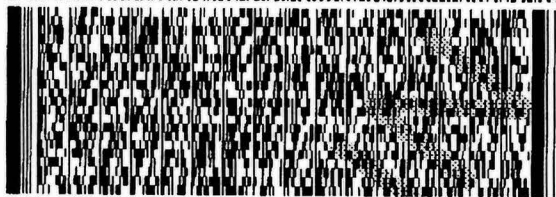
TO SECTION 8(E)  
TSCA CONFIDENTIAL BUSINESS INFO  
EPA EAST - ROOM 6428 US ENVIRONMENTAL  
1201 CONSTITUTION AVENUE, NW  
WASHINGTON DC 200043302

(202) 564-8940 X 3492

REF:

INU:

DEPT:



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Express



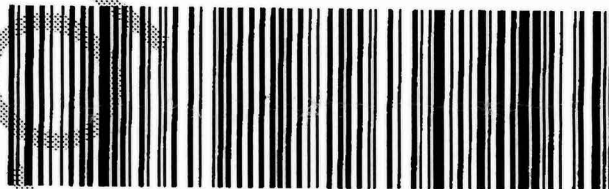
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FRI - 25 MAR 3:00P  
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DC-US IAD





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Writer's Direct Access  
**John B. Dubeck**  
(202) 434-4125  
dubeck@khlaw.com

April 21, 2016

**Via Hand Delivery**

TSCA Confidential Business Information Center (7407M)  
Attn: Section 8(e)  
U.S. Environmental Protection Agency  
1201 Constitution Avenue, NW  
WJC East - Room 6428  
Washington DC 20004-3302

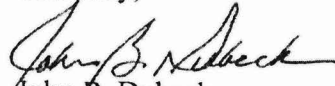
**Re: TSCA 8(e) Submission for Chemical Abstracts Service Registry Numbers  
(CASRN) 375-95-1, 335-67-1, 1763-23-1, 335-76-2, 2058-94-8, and 355-  
46-4; Withdrawal of Confidential Business Information Claims**

Dear Sir or Madam:

On behalf of our client, Solvay Specialty Polymers USA, LLC (Solvay), we are refiling a submission to the U.S. Environmental Protection Agency (EPA) that was made pursuant to Section 8(e) of the Toxic Substances Control Act (TSCA) (15 U.S.C. § 2601 *et seq.*). This filing was dated March 26, 2016, and concerns the substance perfluorononanoic acid (PFNA, CASRN 375-95-1) and several other perfluorinated chemicals (PFCs). Based on discussions with EPA staff in the Office of Pollution Prevention and Toxics, our client is withdrawing the confidential business information (CBI) claims for this submission. We have enclosed a copy of this submission with the CBI claims removed; the content of the submission is otherwise unmodified.

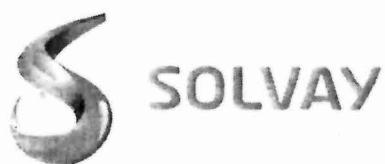
If you have any questions or require additional information on this matter, please do not hesitate to contact me.

Sincerely,

  
John B. Dubeck

Enclosure





**VIA FEDEX**

March 24, 2016

TSCA Confidential Business Information Center (7407M)

WJC East - Room 6428

Attn: Section 8(e)

U.S. Environmental Protection Agency

1201 Constitution Avenue, N.W.

Washington, D.C. 20004-3302

[Confidentiality claim removed]

**Re: TSCA 8(e) Submission; Chemical Abstract Services Registry Numbers  
("CASRN") 375-95-1, 335-67-1, 1763-23-1, 335-76-2, 2058-94-8, and 355-46-4**

Dear Sir/Madam:

Solvay Specialty Polymers USA, LLC (Solvay) is making this submission to the U.S. Environmental Protection Agency (EPA) pursuant to Section 8(e) of the Toxic Substances Control Act ("TSCA", 15 U.S.C. § 2601 *et seq.*). Solvay recently became aware of certain human serum sampling results. These data confirm the well-known fact that a number of perfluorinated chemicals ("PFCs") have become widely dispersed in the environment to the extent that very low levels are present in essentially all human serum. The current data reveal that perfluorononanoic acid ("PFNA", CASRN 375-95-1) is present at levels over the national average in the serum of a small group tested. PFNA was previously used at Solvay's West Deptford, New Jersey, facility; the serum samples have been reported to Solvay as being from residents that obtained their drinking water from private wells in West Deptford Township. [Confidential explanation for prior claim of confidentiality removed.]

Solvay has received only limited information on the individuals tested. Solvay had no role in the selection of the individuals tested or the testing methodology employed. The results of this investigation are only applicable to the individuals tested. The results cannot be generalized to other populations and appear to represent data from two clusters that had distinctly different sources of exposure; whether the exposure of either or both is representative of the local environment is unknown. In addition, these results cannot be used to predict the future occurrence of disease or be associated with current or past health problems. Also, serum PFC concentrations do not provide information about the source of exposure (*i.e.*, water, soil, or food) or how the tested individuals vary with regard to their interactions with different potential exposure pathways.

March 24, 2016

Page 2

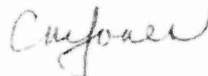
Solvay is reporting these human serum data pursuant to section 8(e) of TSCA despite the fact that Solvay ceased use of PFNA in 2010 and believes it no longer has any obligation under TSCA section 8(e) for PFNA. These data are being submitted based solely on a 2006 EPA guidance document on TSCA section 8(e) reporting that "If the new information on a chemical known to have serious toxic effects indicates a level of exposure previously unknown to the Administrator, it should be reported. Information that corroborates known exposure levels, such as those within the range of chemical blood levels and other biological monitoring data recorded in the [CDC] NHANES (National Health and Nutrition Examination Survey) data base, is not reportable."<sup>1</sup> Consequently, it appears that EPA considers any serum sampling data in excess of the levels reported in the NHANES database as evidence of substantial risk even if those levels, while above the national background, are still so low as to not actually pose a substantial risk. For PFNA, the February 2015 Tables from CDC's *Fourth National Report on Human Exposure to Environmental Chemicals* show a geometric mean of 0.881 µg/L for the latest survey period, 2011-2012.<sup>2</sup>

The serum data obtained by Solvay represent only seven individuals. The PFNA result for each individual in the group exceeds the geometric mean of 0.881 µg/L for the 2011-2012 NHANES survey period. The serum data also include test results for perfluorooctanoic acid (PFOA, CASRN 335-67-1), perfluorooctane sulfonic acid (PFOS, CASRN 1763-23-1), perfluorodecanoic acid (PFDA, CASRN 335-76-2), perfluoroundecanoic acid (PFUnA, CASRN 2058-94-8), and perfluorohexane sulfonic acid (PFHxS, CASRN 355-46-4). Each of the seven individuals has levels in excess of the NHANES mean for at least two of the other five PFCs, as shown by the enclosed table.

Actions taken by Solvay, including the submission of this report, should not be taken to mean that Solvay recognizes or admits there is any health issue with respect to the presence of PFNA or other PFCs in human serum at the detected levels or that Solvay is in any way responsible for these substances if they are found; other sources have contributed to ambient PFC levels in the environment.

If you have any questions or require additional information regarding this submission, please do not hesitate to contact me.

Sincerely,



Charles Jones  
Plant Manager  
Solvay Specialty Polymers USA, LLC

Enclosures

<sup>1</sup> EPA, "Toxic Substances Control Act (TSCA) Section 8(e) Substantial Risk Notifications—Frequent Questions" (Sept. 2006) (Q & A 2), available at <http://www.epa.gov/oppt/tscas8e/pubs/frequentlyaskedquestionsfaqs.html>.

<sup>2</sup> CDC, "Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables" (Feb. 2015), available at [http://www.cdc.gov/biomonitoring/pdf/FourthReport\\_UpdatedTables\\_Feb2015.pdf](http://www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Feb2015.pdf).

[Confidentiality claim removed]

Sample	PFNA (ug/L)	PFOA (ug/L)	PFOS (ug/L)	PFDA (ug/L)	PFUnA (ug/L)	PFHxS (ug/L)
Individual 1	35	29.7	13.6	U 0.5	U 0.5	2.09
Individual 2	55.8	60.8	9.04	U 0.5	U 0.5	3.5
Individual 3	11.5	13.7	2.9	U 0.5	U 0.5	U 1
Individual 4	2.26	2.16	6.69	U 0.5	U 0.5	U 1
Individual 5	7.63	2.31	78.2	2.78	3.58	1.78
Individual 6	5.01	1.61	28	0.812	1.81	1.01
Individual 7	2.05	1.3	9.03	U 0.5	0.898	U 1
NHANES Geometric Mean 2009-2010	1.26	3.07	9.32	0.279	0.172	1.66
NHANES Geometric Mean 2011-2012	0.881	2.08	6.31	0.199	--	1.28

**Bold** values exceed the NHANES geometric mean for the 2011-2012 survey period (2009-2010 for PFUnA, which did not have a 2011-2012 NHANES calculation)

"U" indicates value below the method quantitation limit

